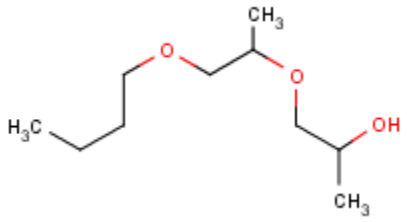
Dipropylene Glycol Monobutyl Ether

(CAS# 29911-28-2)

(Synonyms: 2-(Butoxypropoxy)-2-propanol; 2-Propanol, 1-(2-butoxy-1-methylethoxy)-; 1-(2-Butoxy-1-methylethoxy)propan-2-ol; Dipropylene glycol n-butyl ether; DPnB)



Dipropylene Glycol Monobutyl Ether Acute REL

No acute REL was developed at this time.

Dipropylene Glycol Monobutyl Ether 8-hour REL

Reference Exposure Level	**0.05 mg/m^3 (6 ppb) [Inhalation]**
Critical effects	Histopathological lesions
Hazard Index target	Liver and nasal mucosa

1 Physical and Chemical Properties

Physical form	clear, colorless liquid
Structural formula	C_4-H_9-O-(C_3-H_6-O)$_2$-H
Molecular weight	190.28 g/mole
Density	0.910 g/cm^3
Boiling point	230 ºC
Melting point	< -75 ºC
Vapor pressure	0.06 mm Hg @ 25ºC
Flash point	100.4 ºC
Log K_{OW}	1.523
Water solubility	45,000 mg/L @ 20ºC
Atmospheric half-life	2.6 hrs
Conversion factor	1 ppm = 7.78 mg/m^3

2 Production, Use, and Exposure

Propylene glycol ethers are manufactured by the reaction of propylene oxide with methyl alcohol or n-butyl alcohol. Chain lengths of the products will vary depending on the molar ratio of reactants, the temperature, and the pressure used for the reaction. Monopropylene glycol ethers result from lower molar ratios of propylene oxide to alcohol and milder conditions, whereas increases in propylene oxide, temperatures, and pressures will produce di- and tripropylene glycol mono-alkyl ethers. The estimated production of dipropylene glycol monobutyl ether (DPnB) in 2004 was 14 million pounds (OECD, 2003).

"Uses for DPnB include: coupling agent (i.e., blending facilitator) for cleaners such as degreasers, paint removers, metal cleaners and hard surface cleaners; coalescent for lowering MFFT the minimal film forming temperature) in latex coatings; solvent for water-reducible coatings; chemical intermediate for production of epoxides, acid ester derivatives, solvents, and plasticizers." (OECD, 2003)

The greatest exposure potential exists for commercial workers and other consumers, most likely via inhalation or dermal contact, when coatings are applied to surfaces or when liquid products containing DPnB are otherwise used. Exposure to the general population is also possible through inhalation of ambient air containing DPnB released from industrial processes or through evaporation of coatings or other products containing DPnB. The estimated soil/water-sediment/water partition coefficient for DPnB (K_{OC} = 10) suggests that it has high soil mobility and can leach from soil deposits to groundwater, thereby allowing possible exposure through ingestion of drinking water (OECD, 2003).

3 Pharmacokinetics and Metabolism

Propylene glycol ethers are predominantly metabolized in the liver by two different mechanisms. Mixed function oxidase can cleave the ether bond to yield propylene glycol and an alcohol, which undergoes further metabolism to CO_2 and water. The second mechanism involves the conjugation of the parent propylene glycol ether or its intermediate metabolite with glucuronide, sulfate, or glutathione for ultimate excretion, predominantly in the urine (OECD, 2003).

Zemple et al. (1991, unpublished report cited in OECD, 2003) administered oral doses of approximately 75 and 840 mg ^{14}C-labeled DPnB/kg body weight to 4 Fischer 344 rats per dose. Urine was collected in 12-hour increments, feces in 24-hr increments, and expired air was collected at 6, 12, 24, 36, and 48 hours. At the end of 48 hours, brain, muscle, peri-renal fat, skin, kidney, liver, and the remaining carcass were analyzed for total radioactivity. In a separate study, blood was collected at 0.5, 1, 2, 4, 8, 12, 24, 36, and 48 hours. After 48 hours, 42% of the low dose was excreted in the urine and 42% as ^{14}C-CO_2, while 51% of the high dose was excreted in urine and 35% as ^{14}C-CO_2. Four percent of the low dose and 11% of the high dose were eliminated by fecal excretion. Less than 1% of either dose was detected as expired volatile organics. Eleven percent of the low dose and 7% of the high dose were retained in the tissues and carcass, with liver, bone marrow, and kidneys retaining the highest percentage for both doses. Peak blood levels of ^{14}C activity occurred at 0.5 hours for the low dose and at 4 hours for the high dose. After 48 hours, radioactivity measured in all tissues, including blood, bone marrow, brain, carcass, fat, kidney, liver, muscle, and skin, was less than 1% of the original dose for either dose (Zemple et al. 1991, unpublished report cited in OECD, 2003).

4 Acute Toxicity

Acute mammalian toxicity data were summarized in the Screening Information Data Set for propylene glycol ethers (Table adapted from OECD, 2003) as follows:

Acute rat oral LD_{50}	Acute rat inhalation LC_{50} (4 hr)	Acute rat dermal LD_{50} (24 hr)
4000 mg/kg (95% CL: 3200-4600 mg/kg) Reijnders & Zucker-Keizer 1987 1850 mg/kg, Rowe, 1947 2160 mg/kg (mouse) Algate et al. 1988	> 42.1 ppm* (vapor, measured) (=328 mg/m^3; no deaths) *highest practically attainable vapor concentration Gushow et al. 1987 >2040 mg/m^3 (aerosol, Measured) (=262 ppm; no deaths), Cieszlak et al. 1990	>2000 mg/kg (no deaths) Reijnders 1987

5 Derivation of Acute REL (1-hour exposure)

No studies of short-term exposure to DPnB were located that were appropriate for the derivation of an acute REL. While an LC_{50} was reported, this value represents the upper limit for acute exposures that are compatible with survival without regard to protecting health. As such, an LC_{50} is not the preferred basis for the derivation of an acute REL, which requires consideration of effects much less severe than lethality.

In the course of an 8-hour exposure, intermittent spikes in exposure levels are included in the time-weighted average addressed with the 8-hr REL. The values associated with 8-hr RELs are typically lower than allowed for acute 1-hr exposures, due to the longer exposure duration and possibility of recurring exposures. Therefore application of the 8-hr REL to exposure scenarios involving short-term peaks in concentration should be health protective in most cases.

6 Derivation of 8-Hour REL

This 8-hour REL is derived from a study by Cieszlak et al. (1991, an unpublished report cited in OECD, 2003), in which groups of 5 male and 5 female young adult Fischer 344 rats were exposed to an aerosol atmosphere of 0, 200, 810, or 2010 mg/m^3 (0, 25, 100, or 250 ppm) DPnB by nose-only exposure for 6 hours/day, 5 days/week, over a 2-week period for a total of 9 exposures. All rats survived all the exposures for the duration of the study, with minimal clinical effects observed (lethargy for the first few days). The primary effects from exposure to DPnB were histopathological lesions in the liver and nasal cavities of rats of both sexes at 810 and 2010 mg/m^3 and decreased body weights in both sexes at 2010 mg/m^3, although stress from confinement in the exposure tube contributed to the body weight decreases. There was some slight necrosis in the liver in some instances, but the liver changes were primarily characterized by increased hepatocyte size, which was supported by observed liver weight increases. The nasal cavities exhibited hyperplasia, metaplasia, degeneration, and/or inflammation of the anterior nasal mucosa, which was considered a typical direct response to the irritant properties of DPnB in mucous membranes. The NOAEL for DPnB was determined to be 200 mg/m^3 and the LOAEL was 810 mg/m^3 based on the histopathological changes observed in the liver and nasal mucosa (Cieszlak et al. 1991, unpublished report cited in OECD, 2003). A value of $n = 1$ is used in extrapolating from an experimental exposure duration of less than 8 hours to an 8-hour level.

To account for the possibility of long-term repeated occupational exposures, a subchronic uncertainty factor of 10 is applied since the experimental exposure is < 8% of the expected lifetime of the species tested. The interspecies uncertainty factor is adjusted to 6 (2 * √10) because the U.S. EPA Human Equivalent Concentration procedure is used as a partial adjustment for interspecies toxicokinetic differences. A regional gas dose ratio of 1 is used for gases with systemic effects, where species-specific, but not chemical-specific data were available. An intraspecies toxicokinetic uncertainty factor of 10 is used in consideration of the protection of children's health and sensitive subgroups. This, combined with a subchronic UF of 10, is expected to address residual deficiencies in the database. This decision is further substantiated by the developmental study by Dow Chemical (2006) described below in which the NOAEL and LOAEL values are within 2-3-fold of those reported by Cieszlak. Default values of √10 are used for the interspecies and intraspecies toxicodynamic uncertainty sub-factors in the absence of data to indicate otherwise.

Study	Cieszlak et al. 1991 (in OECD 2003)
Study population	Fischer 344 rats
Exposure method	Nose-only inhalation
Exposure continuity	6 hr/day, 5 d/wk
Exposure duration	2 weeks (9 exposures)
Critical effects	Histopathological lesions in the liver and nasal mucosa
LOAEL	810 mg/m^3
NOAEL	200 mg/m^3
Time-adjusted exposure	$C^n * T = K$, $n = 1$ (ten Berge et al. 1986)
Extrapolated concentration	107 mg/m^3 (200 * 6/8 * 5/7)
Human concentration adjustment	107 mg/m^3 (RGDR = 1; systemic)
LOAEL uncertainty factor (UF_L)	1 (NOAEL observed)
Subchronic uncertainty factor	10
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	2
Toxicodynamic (UF_{A-d})	√10
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	10
Toxicodynamic (UF_{H-d})	√10
Cumulative uncertainty factor	2000
8-hour Reference Exposure Level	**0.05 mg/m^3**

RGDR: regional gas dose ratio

For comparison with the inhalation study by Cieszlak et al. (1991), an oral exposure study reported by Dow Chemical Co. (2006) described mild hepatocellular hypertrophy for which a LOAEL of 300 mg/kg-d and a NOAEL of 100 mg/kg-d were reported. In this study, groups of 12 male and 12 female Sprague-Dawley rats were administered, by gavage, doses of 0 (vehicle), 100, 300, or 1000 mg DPnB/kg-d. Females were dosed once daily for 2 weeks prior to breeding, through breeding (2 weeks), gestation (3 weeks), and lactation up to postpartum day 4, and were

necropsied on postpartum day 5. Males were dosed once daily for 2 weeks prior to breeding and continuing through breeding (2 weeks) until necropsy (test day 29). Treatment-related increases in the incidences of very slight to slight hepatocellular hypertrophy in the liver, relative to controls, were observed in males given 100, 300, or 1000 mg/kg-d DPnB and in females given 300 or 1000 mg/kg-d DPnB. The hepatocellular hypertrophy was characterized by an increase in the size of hepatocytes in a centrilobular/midzonal distribution. Male rats given 300 or 1000 mg/kg-d and females given 1000 mg/kg-d exhibited treatment-related, statistically identified, higher mean absolute and relative liver weights. At 100 mg/kg-d, liver weight changes were identified in males, but were within the historical control range and were not considered treatment-related. However, this study did not examine changes in liver enzymes that may have been indicative of liver damage. Male rats receiving 300 or 1000 mg/kg-d DPnB also exhibited alpha 2μ globulin nephropathy, although this was not considered relevant to human risk assessment because humans do not develop the nephropathy due to quantitative or qualitative differences in this protein. Observations in the offspring occurred at low frequency and bore no relationship to treatment and there were no treatment-related effects on litter size or pup body weights at any dose level tested. While the LOAEL (300 mg/kg-d) and the NOAEL (100 mg/kg-d) in this study are lower than in the study used to calculate the REL, the Ciezlak study was used in preference to this study because the route of exposure was by inhalation.

7 Other Toxicity

Since exposure can occur via dermal contact through the use of products containing DPnB, a brief summary of toxicity studies involving dermal exposure is included. In a 90-day rat dermal study by Lina et al. (1988, unpublished report cited in OECD, 2003), Wistar rats (10/sex/dose) were exposed topically to 0, 91, 273, or 910 mg/kg-day DPnB for 13 weeks (24 hr/day, 5 days/week; non-occluded with collars to prevent self-grooming). Skin irritation occurred at the site of application in all treatment groups, with the irritation being more severe in the high-dose treatment group. Both sexes had increased neutrophils in the mid- and high-dose groups, while only the mid- and high-dose males had decreased body weights. High-dose animals of both sexes had increased liver weights, with alanine and aspartate aminotransferases elevated in males and triglycerides elevated in females. Glucose levels were decreased in high-dose females. Histopathology reflected changes consistent with skin irritation at the site of application but no other microscopic lesions were attributable to DPnB treatment. Testes, prostate, epididymides, and seminal vesicles in males and ovaries, uterus, and vagina in females showed no histopathological damage from exposure to DPnB. The NOAEL from this study was established as 91 mg/kg-day for systemic toxicity and the LOAEL was 273 mg/kg-day based on body weight changes and increased neutrophil counts.

Wilmer and van Marwijk (1988, unpublished report cited in OECD, 2003) performed a developmental toxicity study on Wistar rats, where 0, 273, or 910 mg/kg-d of DPnB were administered to the clipped skin of pregnant rats daily on gestation days 6 through 15. Maternal clinical signs and organ or body weights did not differ between treatment and control groups. Pre- and post-implantation loss, number of viable fetuses, and fetal weights and lengths were comparable between treatment and control groups and no frank abnormalities were observed in skeletal or soft tissue. Therefore, the NOAEL was established as 910 mg/kg-d for maternal, embryo, fetal, and developmental toxicity and a LOAEL was not established.

The possibility of human exposure to DPnB via ingestion of contaminated groundwater or inadvertent ingestion of aerosolized products containing DPnB warrants a brief discussion of its oral toxicity. Thevenaz (1989, unpublished report cited in OECD, 2003) administered 0, 200, 450, or 1000 mg/kg-day DPnB in the diet of Sprague-Dawley rats (20/sex/dose) for 13 consecutive weeks. High-dose males had decreased body weights and enlarged livers without associated histopathology, although clinical chemistry results reflected some slightly elevated parameters of liver injury in the high-dose groups of both sexes. Some urinary parameters of the high-dose animals were also altered. The NOAEL was determined to be 450 mg/kg-day and the LOAEL was 1000 mg/kg-day, based on decreased body weights, increased liver and kidney weights (without histopathology) and slight alterations in clinical chemistry parameters.

8 Environmental Fate

The EPIWIN/APO model (U.S. EPA) estimates that the atmospheric photodegradation half-life of DPnB is 2.6 hours, based on 12 hours of sunlight/day and an average hydroxyl radical concentration of 1.5×10^6 OH/cm^3. The ether linkages of propylene glycol ethers are not expected to easily hydrolyze, therefore the ether groups are generally stable in water under neutral conditions at ambient temperatures. The estimated Henry's Law constant of 2.97×10^{-7} atm-m^3/mole for DPnB indicates it has limited potential to partition from water to air. The environmental distribution of DPnB, as predicted by Mackay Level III fugacity modeling, is 0.827% in air, 50.9% in water, 48.2% in soil, and 0.0947% in sediment. OECD guideline studies indicate that DPnB is readily biodegradable by at least one assay. Therefore, DPnB is unlikely to persist in the environment. With a predicted bioconcentration factor of 1.47 and Log K_{OW} of 1.523, DPnB has very limited potential to bioaccumulate (OECD, 2003).

9 Conclusions

Due to the limited acute toxicity data for DPnB, an acute REL was not calculated, however, the 8-hour REL should be health protective for scenarios involving short-term peaks in concentration. Two 8-hour RELs are presented, one derived from an inhalation study and one from an oral study with route-to-route extrapolation, with an approximately 5-fold difference between the two values. Although the inhalation study is a secondary source described in OECD (2003), it was noted as a GLP-compliant study and provided sufficient detail for the derivation of a REL, as was the oral study provided by Dow Chemical Co. (2006). For this reason, the inhalation study is used for the REL derivation with the oral study considered to be supportive.

10 References

Dow Chemical Co. (2006). Dipropylene glycol n-butyl ether (DPnB): a repeated dose reproduction toxicity screening test in Crl:CD (SD) rats. Report no. K-005474-039. Endpoint study record, IUCLID 5 Database.

OECD (2003). Organization for Economic Co-operation and Development Screening Information Data Set for Propylene Glycol Ethers. http://www.chem.OECD.ch/irptc/sids/OECDSIDS/PGEs.pdf Accessed 08/18/08.

ten Berge WF, Zwart A, and Appelman LM (1986). Concentration-time mortality response relationship of irritant and systematically acting vapours and gases. J Hazard Mater 13: 301-309.